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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/535,268	03/21/2006	Keiji Kubo	08279.1210USWO	3871

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EXAMINER	
MCDOWELL, BRIAN E	
ART UNIT	PAPER NUMBER
1624	
MAIL DATE	DELIVERY MODE
12/01/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/535,268	KUBO ET AL.	
	Examiner	Art Unit	
	BRIAN MCDOWELL	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,6,9-11,13,15-18 and 20-25* is/are pending in the application.

4a) Of the above claim(s) *10,11 and 16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,6,9,13,15,17,18,20-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/21/2009,10/1/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

/BEM/

DETAILED ACTION

The following office action replaces the Ex Parte Quayle mailed 4/1/2009. The Ex Parte Quayle Office Action has been withdrawn.

Status of Claims

Claims 1, 5, 6, 9-11, 13, 15-18, and 20-25 are pending in the instant application. Claims 10, 11, and 16 are withdrawn. An action on the merits of claims 1, 5, 6, 9, 13, 15, 17, 18, and 20-25 is contained herein.

Status of Restriction Requirement

Applicant is reminded that the invention under examination is drawn to group I, wherein compounds of the general formula (I) contain the limitation Y = C(O), X = hydrocarbon, a =2, Z_1 = Z_3 = a bond, and Z_2 = NR^1 and forms a ring with B and simple compositions thereof. As currently amended, the elected specie (example 68 of specification) reads on claims 1, 5, 6, 9, 13, 15, 17, 18, and 20-25. Please amend the claims accordingly.

Status of Specification and Claim Objections

Applicant's amendment and arguments, see Remarks, filed 10/1/2009, with respect to the objections set forth in the Ex Parte Quayle Office Action mailed 4/1/2009, have been fully considered and the objections have been overcome.

New Objections and Rejections

Claim Objections

Claim 1 is objected to because of the ambiguous limitation "that the optionally substituted imidazole ring represented by ring B may have may be taken together". Please correct.

Claim 15 is objected to because of the following informality:
The word "ac cording" should appropriately be written as "according". Please correct.

Applicant is advised that should claim 17 be found allowable, claim 18 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). In the instant case, claims 17 and 18 encompass substituent "Z^3", wherein said substituent is a bond as recited in claim 1. Therefore, subgenus structures Ic and Id are considered equivalent since the imidazolyl portion of formula Ic (see Z^4-N bond) could be rotated on paper to give formula Id.

Claims 21-25 are objected to because of the ambiguous limitation "A pharmaceutical preparation". The examiner assumes that the claims are drawn to pharmaceutical compositions comprising compounds of formula I. If the latter is true and are indeed drawn to pharmaceutical compositions, the claims should be rewritten as "A pharmaceutical composition which comprises the compound according to claim 1 along with an acceptable pharmaceutical carrier" or similar language thereof. Please correct.

Claims 22-25 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. **The for use limitations are not considered and hold no patentable weight.**

Claim Rejections - 35 USC § 112 (2nd Paragraph)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 5, 6, 9, 13, 15, 17, 18, and 21-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In the instant claim 1 and claims which depend on claim 1 (claims 5, 6, 9, 13, 15, 17, 18, and 21-25), applicant recites the limitation "wherein a substituent on ring B *may be* taken together with R^1 to form an optionally substituted ring." However, claim 1 dictates that substituent Z^2 represents $-N(R^1)-$. Thus, if a substituent on ring B together with R^1 does not form an optionally substituted ring, the nitrogen atom in $-N(R^1)-$ would be divalent and the claims would be considered indefinite since nitrogen must have three covalent bonds.

Claim 15 is rejected because of the limitation "wherein Z^3 is independently a divalent linear hydrocarbon group". There is insufficient antecedent basis for this limitation in the claim since claim 1 states that Z^3 is a bond.

Claims 17 and 18 are rejected because the claims refer to a compound according to claim 1 wherein substituents "Z^{2a} and Z^4" are previously defined. There is insufficient antecedent basis for this limitation in the claim since claim 1 does not cite neither substituent "Z^{2a} or Z^4".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5, 6, 9, 13, 15, 17, 18, and 20-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and/or using pharmaceutically acceptable salts of the claimed compounds, does not reasonably provide enablement for *using* non-pharmaceutically acceptable salts of said compounds in the claimed method of use. The specification does not enable any person skilled in the art of synthetic organic chemistry to make the invention commensurate in scope with these claims. "The factors to be considered [in making an enablement rejection] have been summarized as

a) the quantity of experimentation necessary,

b) the amount of direction or guidance presented,

c) the presence or absence of working examples,

d) the nature of the invention,

e) the state of the prior art,

f) the relative skill of those in that art,

g) the predictability or unpredictability of the art,

h) and the breadth of the claims",

In re Colianni, 195 USPQ 150, *Ex parte Forman*, 230 USPQ 546. In the present case the important factors leading to a conclusion of undue experimentation are the absence of any working example, the lack of predictability in the art, and the broad scope of the claims.

a) The instant disclosure does not teach one of ordinary skill how to administer in an efficient and practical manner non-pharmaceutically acceptable salts to a warm-blooded animal in need thereof for treating disease states associated with the inhibition of coagulation factor X (FXa); thus one of ordinary skill would be forced to engage in undue experimentation.

b) The specification does not provide procedural steps or parameters that would serve as direction or guidance concerning using and administering non-pharmaceutically acceptable salts to a warm-blooded animal for treating disease states associated with the inhibition of coagulation factor X (FXa).

c) There are no working examples where applicant's disclosure adequately describes how to use non-pharmaceutically acceptable salts of the instantly claimed compounds of formula I for treating disease states associated with the inhibition of coagulation

factor X (FXa). The absence of any examples, disclosures or guidance regarding the latter is telling.

d) The instant invention relates to imidazole derived piperidines of formula I (as well as pharmaceutically and non-pharmaceutically acceptable addition salts of said compounds) as inhibitors of coagulation factor X (FXa).

f) One would have a Ph. D. degree and several years of industrial experience.

e and g) One of ordinary skill could readily search the current chemical literature and subsequently find a treasure trove of references in preparing both pharmaceutically and non-pharmaceutically acceptable addition salts of biologically active compounds. However, it is well known in the art that non-pharmaceutically acceptable addition salts (e.g., heavy metal and toxic salts) are not acceptable for use in a pharmaceutical setting. The aforementioned salts could not be administered to a mammal orally or intravenously without lethal consequences due to their highly toxic chemical content. Thus, the instantly claimed salts would have no application in a pharmaceutical environment. MPEP states the following:

The enablement requirement refers to the requirement of 35 U.S.C. 112, first paragraph that the specification describe how to make and how to use the invention. The invention that one skilled in the art must be enabled to make and use is that defined by the claim(s) of the particular application or patent. The purpose of the requirement that the specification describe the invention in such terms that one skilled in the art can make

and use the claimed invention is to ensure that the invention is communicated to the interested public in a meaningful way.

h) The breadth of the claims include all of the hundreds of thousands of compounds of formula I as well as every possible addition salt (both pharmaceutically and non-pharmaceutically acceptable salts of said compounds) embraced by the claims. Thus, the scope is egregiously broad.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRIAN MCDOWELL whose telephone number is (571)270-5755. The examiner can normally be reached on Monday-Thursday 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/BRIAN MCDOWELL/
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